(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 November 2002 (07.11.2002)

PCT

(10) International Publication Number
WO 02/087482 A1

(51) International Patent Classification[7]: A61F 13/00

(21) International Application Number: PCT/US02/14073

(22) International Filing Date: 30 April 2002 (30.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/287,875 1 May 2001 (01.05.2001) US
60/292,537 22 May 2001 (22.05.2001) US

(71) **Applicant** *(for all designated States except US)*: **PURDUE PHARMA L.P.** [US/US]; One Stamford Forum, Stamford, CT 06901 (US).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **TAVARES, Lino** [US/US]; 86 South Glen Road, Kinneton, NJ 07405 (US). **REIDENBERG, Bruce** [US/US]; 1 Stonycrest Road, Rye, NY 01580 (US). **SACKLER, Richard** [US/US]; 36th floor, 599 Lexington Avenue, New York, NY 10022 (US). **WRIGHT, Curtis** [US/US]; 1 Jarvis Street, Norwalk, CT 06851 (US). **ALFONSO, Mark, A.** [US/US]; 104 Wedgewood Drive, Easton, CT 06612 (US). **OSHLACK, Benjamin** [US/US]; 351 East 8th Street, Apt. 11B, New York, NY 10028 (US). **CASSIDY, James** [US/US]; 228 Buttonwood Avenue, Cortlandt Manor, NY 10567 (US). **CARPANZANO, Anthony, E.** [US/US]; 20 Hardscrabble Road, Sherman, CT 06784 (US). **GULLAPALLI, Rampurna, Prasad** [IN/US]; 320 Nob Hill Drive, Elmsford, NY 10523 (US). **SHEVCHUK, Ihor** [US/US]; 650 Warburton Avenue, Apt. 2B, Yonkers, NY 10701 (US).

(74) **Agents: ROBINSON, Joseph, R.** et al.; Darby & Darby P.C., P.O. Box 5257, New York, NY 10150-5257 (US).

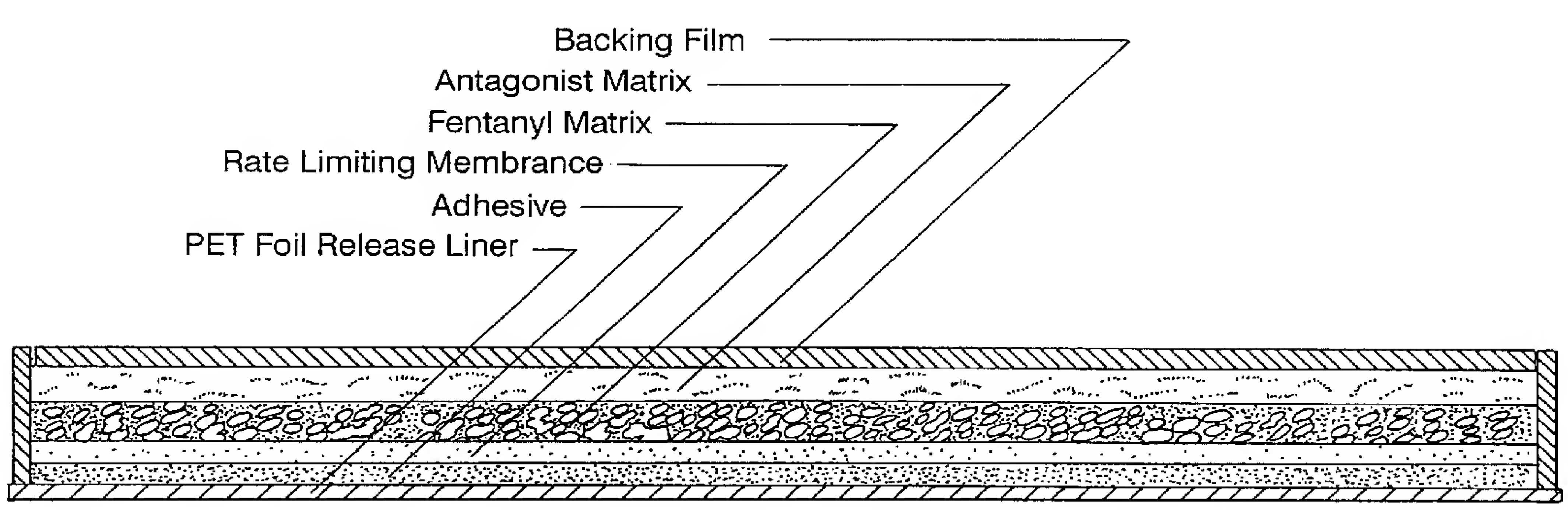
(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** ABUSE RESISTANT OPIOID CONTAINING TRANSDERMAL SYSTEMS



Antagonist and Fentanyl in Different Layers

(57) **Abstract:** The present invention relates to transdermal dosage form (Fig. 1-3) comprising at least one activating agent and at least one inactivating agent. The dosage form (Fig. 1-3) releases the inactivating agent upon disruption of the dosage form (Fig. 1-3) thereby preventing or hindering misuse of the active agent contained in the dosage form (Fig. 1-3).

WO 02/087482 A1

ABUSE RESISTANT OPIOID CONTAINING TRANSDERMAL SYSTEMS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application Serial No. 60/287,875, filed May 1, 2001, and from U.S. Provisional Application Serial No. 60/292,537, filed May 22, 2001, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to a tamper-resistant article and to a transdermal dosage form that prevents misuse of the medicament therein. The dosage form includes at least one inactivating agent that is released when the article or dosage form is misused. Preferably, the inactivating agent is a crosslinking agent that crosslinks or degrades the medicament contained within the article or patch. However, the inactivating agent is not delivered to a patient by the transdermal route. In addition, the article or patch may further include an antagonist, *e.g.*, an opiate antagonist, to reduce abuse of the medicament in the dosage form.

BACKGROUND OF THE INVENTION

Transdermal dosage forms are convenient dosage forms for delivering many different active therapeutically effective agents, including but not limited to analgesics, such as for example, opioid analgesics. Typical opioid analgesics include, but are not limited to, fentanyl, buprenorphine, etorphines, and other high potency narcotics. Typical non-opioid drugs which are delivered by the transdermal route are anti-emetics (scopolamine), cardiovascular agents (nitrates & clonidine) and hormones (estrogen & testosterone).

The most common transdermal dosage form is a diffusion-driven transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Other transdermal dosage forms include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontohoretic (electrical diffusion) delivery system.

Transdermal dosage forms are particularly useful for timed release and sustained release of active agents. However, many dosage forms, and particularly those for timed and sustained release of active agent(s), contain large amounts of active agent(s), often many times the actual absorbed dose. Often, the dosage form contains an excess of active agent or delivers less than the entire amount of its active agent to the subject being treated. This results in some of the active agent remaining in the dosage form after use. Both the unused dosage form and the portion of active agent that remains in the dosage form after use are subject to potential illicit abuse, particularly if the active agent is a narcotic or a controlled substance. For example, used dosage forms containing excess or unused opioids may be tampered with by chewing or extraction by a drug abuser. Even careful disposal of used dosage forms may not be completely effective in preventing abuse, particularly in cases of incomplete or partial compliance.

U.S. Patent No. 5,149,538 to Granger *et al.* ("Granger") relates to a misuse-resistive dosage form for the transdermal delivery of opioids.

There is a need for a transdermal dosage form that is less susceptible to abuse by misuse of the active agent remaining in an unused dosage unit or in a used dosage unit, *i.e.*, residual active agent.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1. A schematic of a Fentanyl transdermal system design where the antagonist and Fentanyl are in separate layers.

Figure 2. A schematic of a Fentanyl transdermal system design where the antagonist and barrier are printed on backing film.

Figure 3. A schematic of a Fentanyl transdermal system design where the coated/complexed antagonist is present in a Fentanyl/adhesive matrix.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a transdermal dosage form, *e.g.,* a transdermal patch, wherein the dosage form includes at least one activating agent and at least one inactivating agent. The inactivating agent is released only when the dosage form is solubilized, opened, chewed and/or cut apart, but it is not transdermally delivered to the patient. Therefore, the article or composition prevents or hinders misuse of the active agent contained in the transdermal dosage form. In a preferred embodiment, the inactivating agent is a crosslinking agent. In a further embodiment, the crosslinking agent is selected from the group consisting of polymerizing agent, photoinitiator, and aldehydes (*e.g.,* formalin). Preferably, the polymerizing agent is selected from the group consisting of diisocyanate, organic peroxide, diimide, diol, triol, epoxide, cyanoacrylate, and a UV activated monomer. In an additional embodiment, the dosage form further comprises an antagonist, preferably an opiate antagonist.

The present invention contemplates a transdermal dosage article or a transdermal dosage composition comprising (1) a matrix comprising at least one active agent and (2) beads comprising at least one inactivating agent, wherein the beads are mixed into the matrix. The beads may further comprise an antagonist. In a specific embodiment, the beads are comprised of microscopic polysaccharide beads, starch beads, polyactate beads, or liposomes. In a further embodiment, the beads are dissolved upon contact with an aqueous solvent or a non-aqueous solvent.

The present invention further contemplates a transdermal dosage article or a transdermal dosage composition comprising (1) a matrix comprising at least one active agent and (2) a polymer complexed to at least one inactivating agent. In a further embodiment, the polymer also may be complexed to at least one antagonist. In a specific embodiment, the polymer is a crosslinked styrene divinyl benzene polymer. The polymer may optionally be

linked to a solid support, such as a resin. In a further embodiment, the inactivating agent and the antagonist uncomplex from the polymer in an ionic solvent.

The present invention further contemplates a transdermal dosage article comprising (1) a first layer comprising at least one active agent, (2) an inactivating layer comprising at least one inactivating agent, and (3) a solvent soluble membrane or solvent soluble layer. In a further embodiment, the inactivating layer further comprises an antagonist. In a specific embodiment, the solvent soluble membrane or solvent soluble layer is comprised of hydroxy ethyl cellulose and hydroxypropylmethylcellulose. In a further embodiment, the solvent is water.

DETAILED DESCRIPTION

The present invention provides a transdermal dosage form, *e.g.,* a transdermal patch or composition, wherein the dosage form includes at least one inactivating agent. The dosage form may further comprise at least one antagonist. The inactivating agent and the antagonist may be present in different portions of the dosage form or may be present in a combination. The combination of the inactivating agent and antagonist may be included in any part of the transdermal dosage form, such as in an adhesive coating present in a transdermal patch. The inactivating agent and/or antagonist are released only when the dosage form is solubilized, opened, chewed or cut apart. The inactivating agent and the antagonist are sequestered within the transdermal dosage form and are not transdermally delivered to the patient. Therefore, during storage and regular use, the inactivating agent and antagonist are not in direct contact or are not in sufficient contact with the activating agent to render the active agent inactive. However, if the dosage form is misused for the purpose of being abused, such as for example, is chewed, soaked, subjected to extraction, smoked, or the like, the inactivating agent and/or the antagonist are released. The inactivating agent would degrade or cross-link the medicament or active agent to decrease its efficacy. Additionally, the antagonist would block the effects produced by the activating agent. The present invention further discloses methods of preparing such abuse resistant dosage forms.

Transdermal dosage forms may be classified into transdermal dosage articles and transdermal dosage compositions. The most common transdermal dosage article is a diffusion-driven transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Transdermal dosage compositions include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and ionthoretic (electrical diffusion) delivery system. Preferably, the transdermal dosage form is a

transdermal patch. The dosage form contains both at least one active agent and at least one first inactivating agent.

As used herein, the terms "active agent" or "activating agent" refer to a compound that produces a pharmacological effect that leads to a physiological change. Non-limiting examples of active agents which may be used in the present invention are fentanyl, buprenorphine, etorphine and related opioids of sufficient potency to allow transdermal usage, or any combinations thereof. Non-opioid drugs that may be used include, but are not limited to, anti-emetics (scopolamine), cardiovascular agents (nitrates & clonidine) and hormones (estrogen & testosterone). In a specific embodiment of the present application, the active agent is an opioid analgesic used in the treatment of pain. Most preferably, the active agent is fentanyl.

As used herein, the term "antagonist" refers to a compound that renders the active agent unavailable to produce a pharmacological effect. In other words, the antagonist, itself, does not produce a pharmacological effect, but rather blocks the effects of an active agent. In a specific embodiment, the antagonist interacts with the same receptor as the active agent and inhibits the interaction of the active agent with the receptor. Non-limiting examples of antagonists include opioid-neutralizing antibodies; narcotic antagonists such as naloxone, naltrexone and nalmefene; dysphoric or irritating agents such as scopolamine, ketamine, atropine or mustard oils; or any combinations thereof. In a preferred embodiment, the antagonist is naloxone or naltrexone.

As used herein, the term "inactivating agent" refers to a compound that inactivates or crosslinks the medicament, in order to decrease the abuse potential of the transdermal dosage form. Non-limiting examples of a inactivating agents include, but are not limited to, polymerizing agents, photoinitiators, and formalin. Examples of polymerizing agents include diisocyanates, peroxides, diimides, diols, triols, epoxides, cyanoacrylates, and UV activated monomers.

Transdermal Dosage Systems

Any dosage form that is capable of sequestering an inactivating agent and allows for the release of these agents under abuse conditions is contemplated by the present invention. These systems may further comprise an antagonist. Such transdermal dosage systems include, but are not limited to, solvent-based systems, ion-concentration based systems, and

barrier systems.

A solvent-based system can be used to release the inactivating agent only under contact with specific solvents. Such solvents include, but are not limited to, a salt solution, ether, dimethylfuran, alcohol, chloroform, acetone, benzene, dimethylformamide, methylene chloride, toluene, formaldehyde, ethyl acetate, celusolve; cosmetic agents such as, nail polish remover and glycerine; paint/printing agents such as, methyl ethyl ketone, mineral spirits, turpentine; fuels such as, gasoline and kerosene; dry cleaning fluids; or an aqueous solvent similar to saliva. The solvent-based system is comprised of microscopic beads that are porous to the solvents. The beads that can be used in the invention include, but are not limited to, microscopic polysaccharide beads; starch beads; polylactate beads; polylactategluconate beads (PLGA);beads made from mineral based microporous catalyst materials such as zeolite, alumina, hydroxyapetite, and silica; beads made from hydrogels such as polyethyleneoxide, polyacrylamide, and polyvinylpyrolidone; beads made from chromatography media such as ion exchange resins, size exclusion beads, and affinity resins; beads made from natural source gels such as chitosan, gelatin, celluloses, and agarose; and beads made from sintered porous supports/filters such as brass, aluminum, and glass. In a specific embodiment, the beads are microscopic polysaccharide beads; starch beads; or polyactate beads. The solvent-based system may also use liposomes. The release of the inactivating agent is dependent upon the chemical properties of the bead or liposome used in the present invention. For example, when starch beads are used, the inactivating agent is released when contacted with an aqueous environment.

An ion-concentration based system can be used to preferentially release the inactivating agent when contacted with an ionic solvent. In such a system, the agent would be complexed or bound to an exchange resin present in the dosage form. The resin can be of any form known in the art. The exchange resin may be comprised of at least one resin selected from the group consisting of styrene divinylbenzene, an acrylic matirix with an anion and/or cation functional groups, and a silica matrix with anion and/or cation functional groups. Preferably the resin is a crosslinked styrene divinyl benzene polymer or a cation exchange resin, *e.g.* Amberlite IR-122. Functional groups may include, but are not limited to, $R-CH_2N^+(CH_3)_3$; $R-CH_2N^+(CH_3)_2C_2H_4OH$; $R-SO_3-$; $R-CH_2N^+H(CH_3)_2$; $R-CH_2COO-$; $R-COO-$; and $R-CH_2N(CH_2COO)_2$. When the dosage form is contacted with an ionic solvent, such as an alcohol or water, the agent would be released. In one embodiment, the solvent contains ethanol and water. In a specific embodiment, the ion concentration of the solvent needed to

release the first inactivating agent is about 100 mEq/liter. To further ensure dissociation in the saliva, the resin can be further constructed to be cleaved by salivary enzymes such as, but not limited to, salivary amylase.

A layered based system comprises a dosage form in which the active agent and the inactivating agent are present in different layers of the dosage form. For example, the active agent is in a first matrix layer and the inactivating agent is in an inactivating matrix layer of the dosage form or vice versa. The layers may be separated by a barrier, such as a solvent soluble layer or a solvent soluble membrane. The barrier may be soluble in ether, dimethylfuran, alcohol, chloroform, acetone, benzene, dimethylformamide, methylene chloride, toluene, formaldehyde, ethyl acetate, celusolve; cosmetic agents such as, nail polish remover and glycerine; paint/printing agents such as, methyl ethyl ketone, mineral spirits, turpentine; fuels such as, gasoline and kerosene; dry cleaning fluids; or an aqueous solvent similar to saliva. In a specific embodiment, the barrier is soluble in water, alcohol, ether, chloroform, and dimethylfuran. The barrier may be comprised of any material known in the art, such as cellulose film. The barrier may take the form of an adhesive layer, such as, but not limited to, a (hydro)gel layer, polymer based film, woven or non-woven support, porous sponge material, dispersed coated particles or beads. Additionally, the barrier can be protected by a poly(ethylene terephthlate) (PET) release liner. Dosage forms wherein the inactivating agent is in a reservoir also are contemplated by the present invention. As previously discussed, an antagonist also may be present in the inactivating layer.

A transdermal patch produced according to the present invention may be produced in three different forms. In one embodiment, a matrix comprising the inactivating agent is coated onto a backing film. The active agent is then coated onto this matrix. This dosage form then optionally comprises a barrier, an adhesive layer, and a PET release liner. In another embodiment, the inactivating agent is coated onto a backing film. This layer is then separated from a matrix comprising the active agent by a water soluble layer. This dosage form then optionally comprises an adhesive layer and a PET release liner. In another embodiment, a matrix comprising the active agent and the inactivating agent is coated onto a backing film. This matrix may optionally comprise an adhesive. This dosage form may further comprise a barrier, an adhesive, and a PET release liner.

Methods for Preparing Transdermal Dosage Systems

The inactivating agent and antagonist may be incorporated in the transdermal dosage

form by any methods that are known in the art. Listed herein are a few of the preferred methods for incorporating the first inactivating agent into the dosage form. Additionally discussed are the proposed methods of how the formulations would prevent abuse of the dosage form.

Solvent-based System

In one method, microscopic polysaccharide beads are impregnated with at least one inactivating agent. The beads would be physically mixed into (a) the active agent matrix that is to be present on the surface of the transdermal dosage article or (b) the transdermal dosage composition. The beads that can be used in the invention include, but are not limited to, microscopic polysaccharide beads; starch beads; polyactate beads; beads made from mineral based microporous catalyst materials such as zeolite, alumina, hydroxyapetite, and silica; beads made from hydrogels such as polyethyleneoxide, polyacrylamide, and polyvinylpyrolidone; beads made from chromatography media such as ion exchange resins, size exclusion beads, and affinity resins; beads made from natural source gels such as chitosan, gelatin, celluloses, and agarose; and beads made from sintered porous supports/filters such as brass, aluminum, and glass. In a specific embodiment, the beads are microscopic polysaccharide beads; starch beads; and polyactate beads. The bead may further be impregnated with at least one antagonist. The inactivating agent and antagonist would be released when the article or composition are placed in an aqueous environment, such as when the dosage form is chewed or is subject to extraction.

In another method, starch beads are impregnated with at least one inactivating agent. These beads would be susceptible to any enzymes that are present in the saliva, such as salivary amylase. Additionally, the beads may be susceptible to the moisture present in saliva. This moisture would dissolve the beads. These beads would be mixed into (a) the active agent matrix present on the surface of the transdermal dosage article or (b) the transdermal dosage composition. These beads would be dissolved by the moisture or the salivary enzymes when the article or composition is subjected to saliva via buccal or sublingual placement or when swallowed. The starch beads may be further impregnated with at least one antagonist.

In an additional method, layers of at least one inactivating agent would be incorporated into the physical structure of beads. These beads would be mixed into (a) the active agent matrix present on the surface of the transdermal dosage article or (b) the

transdermal dosage composition. The beads that can be used in the invention include, but are not limited to, microscopic polysaccharide beads; starch beads; polyactate beads; beads made from mineral based microporous catalyst materials such as zeolite, alumina, hydroxyapetite, and silica; beads made from hydrogels such as polyethyleneoxide, polyacrylamide, and polyvinylpyrolidone; beads made from chromatography media such as ion exchange resins, size exclusion beads, and affinity resins; beads made from natural source gels such as chitosan, gelatin, celluloses, and agarose; and beads made from sintered porous supports/filters such as brass, aluminum, and glass. In a specific embodiment, the beads are polysaccharide beads and polyacetate beads. In a further embodiment an antagonist is incorporated into the beads. The layers that are incorporated into the beads may represent different forms (*e.g.,* HCl salt, basic form) of the inactivating agent and/or antagonist. These beads can be solubilized in an aqueous and non-aqueous medium.

In one method liposomes comprising at least one inactivating agent are mixed into (a) the active agent matrix present on the surface of the transdermal dosage article or (b) the transdermal dosage composition. In one embodiment, an antagonist is also present. The liposomes may be plain (no protein content) or pore studded (contains protein). The liposomes can be made by any method known in the are. Pore studded liposomes can be constructed with proteinaceous molecular probes that would release the first inactivating agent and the second inactivating agent upon exposure to an aqueous solvent. Comparatively, plain liposomes would release the inactivating agent and antagonist when either exposed to non-aqueous solvents or when exposed to aqueous solvents and physically stressed.

Ion-concentration Based System

A pharmaceutically approved cation exchange resin can be used to produce an alternative transdermal dosage system. The resin can be of any form known in the art. The exchange resin may be comprised of at least one resin selected from the group consisting of styrene divinylbenzene, an acrylic matirix with an anion and/or cation functional groups, and a silica matrix with anion and/or cation functional groups. Preferably the resin is a crosslinked styrene divinyl benzene polymer, a cation exchange resin, *e.g.* Amberlite IR-122, or an anion exchange resin, *e.g.,* Amberlite IRA-900. Functional groups may include, but are not limited to, $R\text{-}CH_2N^+(CH_3)_3$; $R\text{-}CH_2N^+(CH_3)_2C_2H_4OH$; $R\text{-}SO_3\text{-}$; $R\text{-}CH_2N^+H(CH_3)_2$; $R\text{-}CH_2COO\text{-}$; $R\text{-}COO\text{-}$; and $R\text{-}CH_2N(CH_2COO)_2$. The resin may optionally be linked to the surface of a transdermal dosage article, such as a transdermal patch. Styrene divinyl benzene polymer

would complex or bind basic forms of the inactivating agent. In one embodiment, an antagonist is complexed. In the presence of a highly anionic environment, such as saliva, the inactivating agent and antagonist will be released. Comparatively, a resin that binds an acidic form of the inactivating agent and the antagonist, such as an anion exchange resin *e.g.* Amberlite IRA-900, would release the agents in a highly cationic environment, such as gastric fluid. Such gastric fluid may be present in the esophagus, stomach, or duodenum.

Layer Based System

In this system, a layer of at least one inactivating agent is applied to one side of the transdermal dosage article. The layer may further comprise an antagonist. This layer than can be separated from the active agent by a solvent soluble layer or a solvent permeable microporous membrane. In a specific embodiment, the solvent is water. The water soluble layer may be comprised of any substance that may be soluble in a specific solvent, such as hydroxy ethyl cellulose and hydroxypropylmethylcellulose. The layer of the inactivating agent may be applied to the transdermal dosage form by any method known in the art. In one embodiment, the inactivating agent can be applied to the dosage form by 3-dimensional printing technology. Once the inactivating layer is placed on the dosage form, the soluble membrane or layer is placed in contact with it. The active agent then may be applied, by any method to the soluble membrane or layer. When the dosage form is placed into an aqueous solvent, the soluble membrane or layer may dissolve and the inactivating agent is released.

Pharmaceutical Compositions

The compounds of the present invention may be formulated into a pharmaceutical composition. The pharmaceutical composition also may include additives, such as a pharmaceutically acceptable carrier, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrant, an excipient, a diluent, a lubricant, a plasticizer, an edible oil or any combination of any of the foregoing.

Suitable pharmaceutically acceptable carriers include, but are not limited to, ethanol; water; glycerol; aloe vera gel; allantoin; glycerin; vitamin A and E oils; mineral oil; PPG2 myristyl propionate; vegetable oils and solketal.

Suitable binders include, but are not limited to, starch; gelatin; natural sugars, such as glucose, sucrose and lactose; corn sweeteners; natural and synthetic gums, such as acacia,

tragacanth, vegetable gum, and sodium alginate; carboxymethylcellulose; polyethylene glycol; waxes; and the like.

Suitable disintegrators include, but are not limited to, starch such as corn starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Suitable lubricants include, but are not limited to, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

A suitable suspending agent is, but is not limited to, bentonite.

Suitable dispersing and suspending agents include, but are not limited to, synthetic and natural gums, such as vegetable gum, tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone and gelatin.

Suitable edible oils include, but are not limited to, cottonseed oil, sesame oil, coconut oil and peanut oil.

Examples of additional additives include, but are not limited to, sorbitol; talc; stearic acid; and dicalcium phosphate.

Unit Dosage Forms

The pharmaceutical compositions may be formulated as unit dosage forms, such as metered aerosol or liquid sprays, drops, topical gels, topical creams, lotions, ointments, transmucosal systems and devices, iontohoretic (electrical diffusion) delivery system, and transdermal patches.

Topical preparations typically contain a suspending agent and optionally, an antifoaming agent. Such topical preparations may be liquid drenches, alcoholic solutions, topical cleansers, cleansing creams, skin gels, skin lotions, and shampoos in cream or gel formulations (including, but not limited to aqueous solutions and suspensions).

Administration

The dosage forms of the present invention may be used treat various conditions depending on the medicament contained within the dosage form. In a preferred embodiment, the medicament is used to treat pain. The dosage forms of the present invention may be administered alone at appropriate dosages defined by routine testing in order to obtain optimal activity while minimizing any potential toxicity.

The amount of active agent in a dosage form will depend upon the needs of the patient and the characteristics of the patient such as, for example, height, weight, age, and gender.

Such amounts can be determined by those skilled in the art by methods such as establishing a matrix of amounts and effects. However, such amounts should be those amounts effective to achieve the results sought through the dosage form. For example, the amount of an opioid analgesic active agent in such a dosage form should be that amount effective to deliver analgesia to a patient for the amount of time for which the dosage form is to be used.

The amounts of the inactivating active agent and antagonist will depend upon the active agent and the amount of residual active agent that is expected in a particular dosage form. Such amounts can also be determined by those skilled in the art by methods such as establishing a matrix of amounts and effects. However, such amounts should be those amounts effective to achieve the results sought, *i.e.*, inactivation of the residual active agent or the rendering of undesirable of an attractive drug of abuse.

Testing Methods for Transdermal Articles and Compositions

Any method may be used to assess the tamper-resistance of the present invention. In a specific embodiment, the active agent will be extracted from the transdermal article or composition with a solvent. Such solvents include, but are not limited to, a salt solution, ether, dimethylfuran, alcohol, chloroform, acetone, benzene, dimethylformamide, methylene chloride, toluene, formaldehyde, ethyl acetate, celusolve; cosmetic agents such as, nail polish remover and glycerine; paint/printing agents such as, methyl ethyl ketone, mineral spirits, turpentine; fuels such as, gasoline and kerosene; dry cleaning fluids; or an aqueous solvent similar to saliva. After extraction, the active agent present in the solvent and in the article or composition will be assessed using any method known in the art. Such methods include, measurement with infrared or ultraviolet/visible spectrophotometry, chromatography techniques such as high performance liquid chromatography or gas chromatography. The technique should both identify and quantify the active agent in the phosphate buffer and in the composition or article.

In another specific embodiment, the transdermal article will be mechanically separated. A small animal surgeon will be provided the schematics of the test transdermal article. The surgeon, using operating room tools, will then dissect the patch to separate the material containing the active agent from the inactivating agent. The surgeon may be provided with test patches for practice. The test may be timed. After separation, chemical analysis will be performed on the separated materials to determine the degree of success. Any method known in the art may be used for chemical analysis. Such methods include,

measurement with infrared or ultraviolet/visible spectrophotometry, chromatography techniques such as high performance liquid chromatography or gas chromatography.

EXAMPLES

The present invention will be better understood by reference to the following Examples, which are provided as exemplary of the invention, and not by way of limitation.

EXAMPLE I: EXTRACTION IN ETHANOL CONTAINING SOLVENT

The transdermal patch is macerated with 100 mL of a solvent containing 75% ethanol. The patch is macerated for 30 minutes. The drugs that are present in the solvent and in the patch are measured by high performance liquid chromatography.

EXAMPLE II: EXTRACTION IN ETHER CONTAINING SOLVENT

The transdermal patch is macerated with 100 mL of a solvent containing reagent grade diethyl ether. The patch is macerated for 30 minutes. The drugs that are present in the solvent and in the patch are measured by high performance liquid chromatography.

EXAMPLE III: MECHANICAL SEPARATION

A small animal surgeon is provided the schematics of the test transdermal dosage form. The surgeon, using operating room tools, dissects the patch to separate the material containing the active agent from the inactivating agent. The surgeon is provided with two test patches for practice. The time limit for the actual experiment is 1 hour. Chemical analysis is performed on the separated materials to determine the degree of success. The drugs that are present are measured by high performance liquid chromatography.

EXAMPLE IV: EXTRACTION OF AGENTS IN AQUEOUS SOLVENT TO DUPLICATE SALIVA

A transdermal patch is prepared, wherein the patch comprises an active agent and inactivating agent. The patch is placed in a roller bottle, with the adhesive side facing the solvent. The solvent is a 0.5 N NaCl solution that is buffered to pH = 6.4 with a phosphate buffer. About 15 mL of the solvent is placed in the bottle and the bottle then is rolled at 20 rpm for 30 minutes. The drugs that are present in the solvent and in the patch are measured by high performance liquid chromatography.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Patents, patent applications, publications, procedures, and the like are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties.

CLAIMS

WHAT IS CLAIMED IS:

1. A transdermal dosage form comprising at least one active agent and at least one inactivating agent, wherein the inactivating agent is a cross-linking agent that is released upon disruption of the dosage form.

2. A transdermal dosage form of claim 1, wherein the transdermal dosage form is a transdermal patch.

3. A transdermal dosage form of claim 1, wherein the disruption of the dosage form occurs when the dosage form is solubilized, opened, chewed and/or cut apart.

4. A transdermal dosage form of claim 1, wherein the crosslinking agent is selected from the group consisting of polymerizing agent, photoinitiator, and aldehydes.

5. A transdermal dosage form of claim 4, wherein the aldehyde is formalin.

6. A transdermal dosage form of claim 4, wherein the polymerizing agent is selected from the group consisting of diisocyanate, organic peroxide, diimide, diol, triol, epoxide, cyanoacrylate, and a UV activated monomer.

7. A transdermal dosage form of claim 1 further comprising an antagonist.

8. A transdermal dosage form of claim 7, wherein the antagonist is an opiate antagonist, and the active agent is an opiate.

9. A transdermal dosage form comprising a matrix comprising at least one active agent and beads comprising at least one inactivating agent, wherein the beads are mixed into the matrix.

10. A transdermal dosage form of claim 9, wherein the transdermal dosage form is a transdermal dosage article or a transdermal dosage composition.

11. A transdermal dosage form of claim 9 further comprising an antagonist.

12. A transdermal dosage form of claim 9, wherein the beads are comprised of microscopic polysaccharide beads, starch beads, polyacetate beads, or liposomes.

13. A transdermal dosage form of claim 9, wherein the beads are dissolved upon contact with an aqueous solvent or a non-aqueous solvent.

14. A transdermal dosage form comprising a matrix comprising at least one active agent and a polymer complexed to at least one inactivating agent.

15. A transdermal dosage form of claim 14, wherein the transdermal dosage form is a transdermal dosage article or a transdermal dosage composition.

16. A transdermal dosage form of claim 14, wherein the polymer may be complexed to at least one antagonist.

17. A transdermal dosage form of claim 14, wherein the polymer is a crosslinked styrene divinyl benzene polymer.

18. A transdermal dosage form of claim 14, wherein the polymer may optionally be linked to a solid support.

19. A transdermal dosage form of claim 18, wherein the solid support is resin.

20. A transdermal dosage form of claim 14, wherein the inactivating agent and the antagonist uncomplex from the polymer in an ionic solvent.

21. A transdermal dosage article comprising a first layer comprising at least one active agent, an inactivating layer comprising at least one inactivating agent, and a solvent soluble membrane or solvent soluble layer.

22. A transdermal dosage form of claim 21, wherein the inactivating layer further comprises an antagonist.

23. A transdermal dosage form of claim 21, wherein the solvent soluble membrane or solvent soluble layer is comprised of hydroxy ethyl cellulose and hydroxypropylmethylcellulose.

24. A transdermal dosage form of claim 21, wherein the solvent is water.

25. A transdermal dosage form comprising at least one active agent and means for crosslinking said active agent upon disruption of the dosage form.

26. A transdermal dosage form of claim 25 wherein the transdermal dosage form is a transdermal patch.

27. A transdermal dosage form of claim 25 wherein said crosslinking means is a crosslinking agent that is released upon disruption of the dosage form.

28. A transdermal dosage form of claim 25, wherein the disruption of the dosage form occurs when the dosage form is solubilized, opened, chewed and/or cut apart.

29. A transdermal dosage form of claim 25, wherein the crosslinking agent is selected from the group consisting of polymerizing agent, photoinitiator, and aldehydes.

30. A transdermal dosage form of claim 29, wherein the aldehyde is formalin.

31. A transdermal dosage form of claim 29, wherein the polymerizing agent is selected from the group consisting of diisocyanate, organic peroxide, diimide, diol, triol, epoxide, cyanoacrylate, and a UV activated monomer.

32. A transdermal dosage form of claim 25 further comprising an antagonist.

33. A transdermal dosage form of claim 32, wherein the antagonist is an opiate antagonist, and the active agent is an opiate.

34. A transdermal dosage form comprising a matrix comprising at least one active agent and a polymer complexed to at least one inactivating means.

35. A transdermal dosage form of claim 34, wherein the transdermal dosage form is a transdermal dosage article or a transdermal dosage composition.

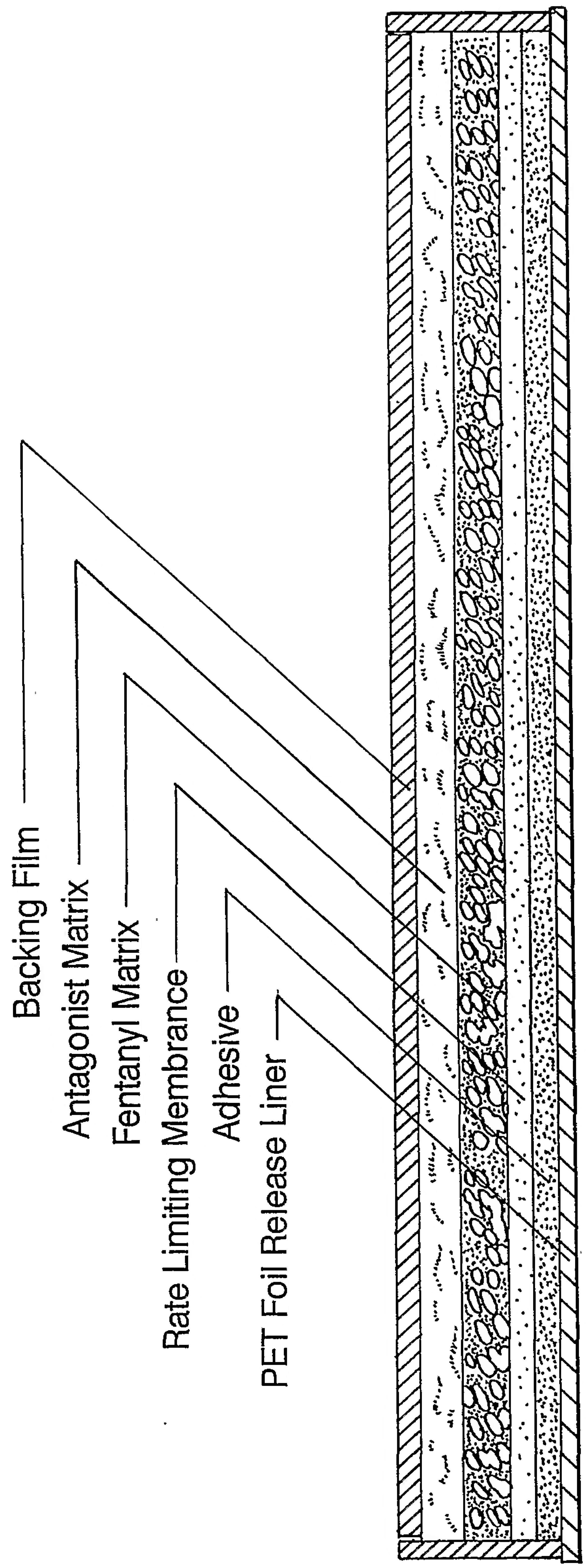
36. A transdermal dosage form of claim 34, wherein the polymer may be complexed to at least one antagonist.

37. A transdermal dosage form of claim 34, wherein the polymer is a crosslinked styrene divinyl benzene polymer.

38. A transdermal dosage form of claim 34, wherein the polymer may optionally be linked to a solid support.

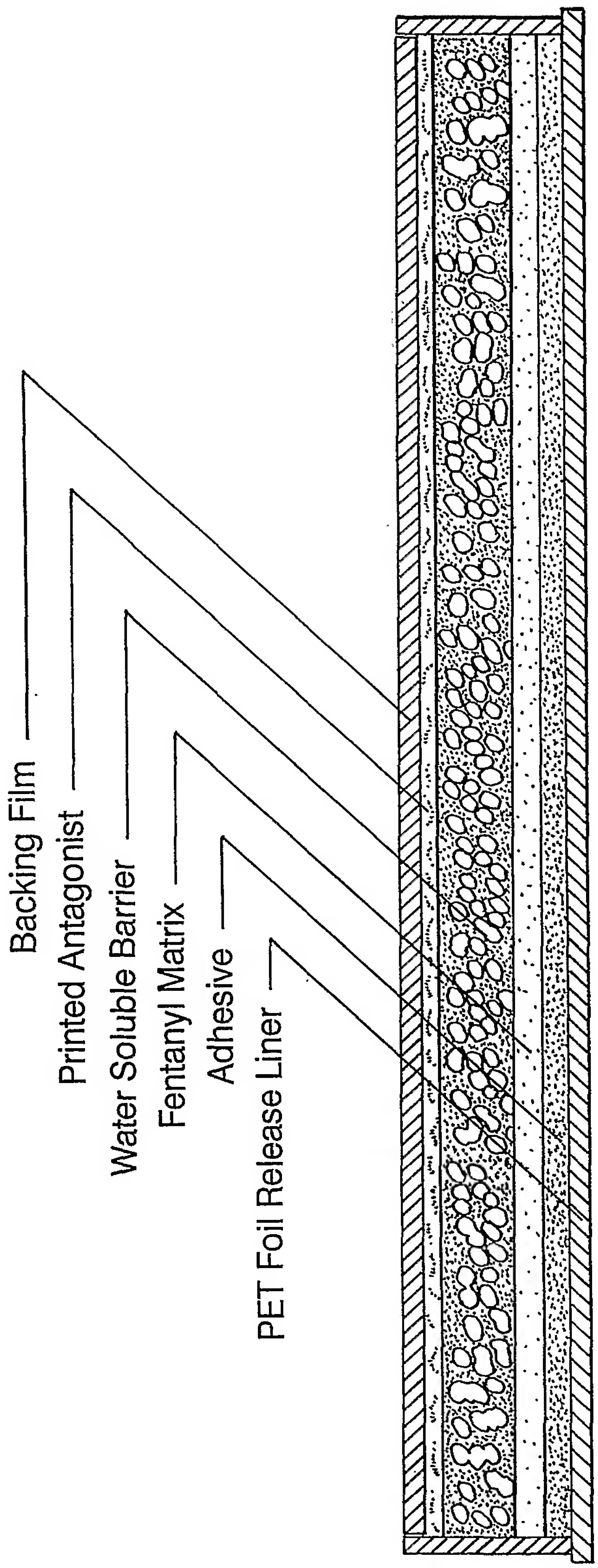
39. A transdermal dosage form of claim 38, wherein the solid support is resin.

40. A transdermal dosage form of claim 34, wherein the inactivating agent and the antagonist uncomplex from the polymer in an ionic solvent.



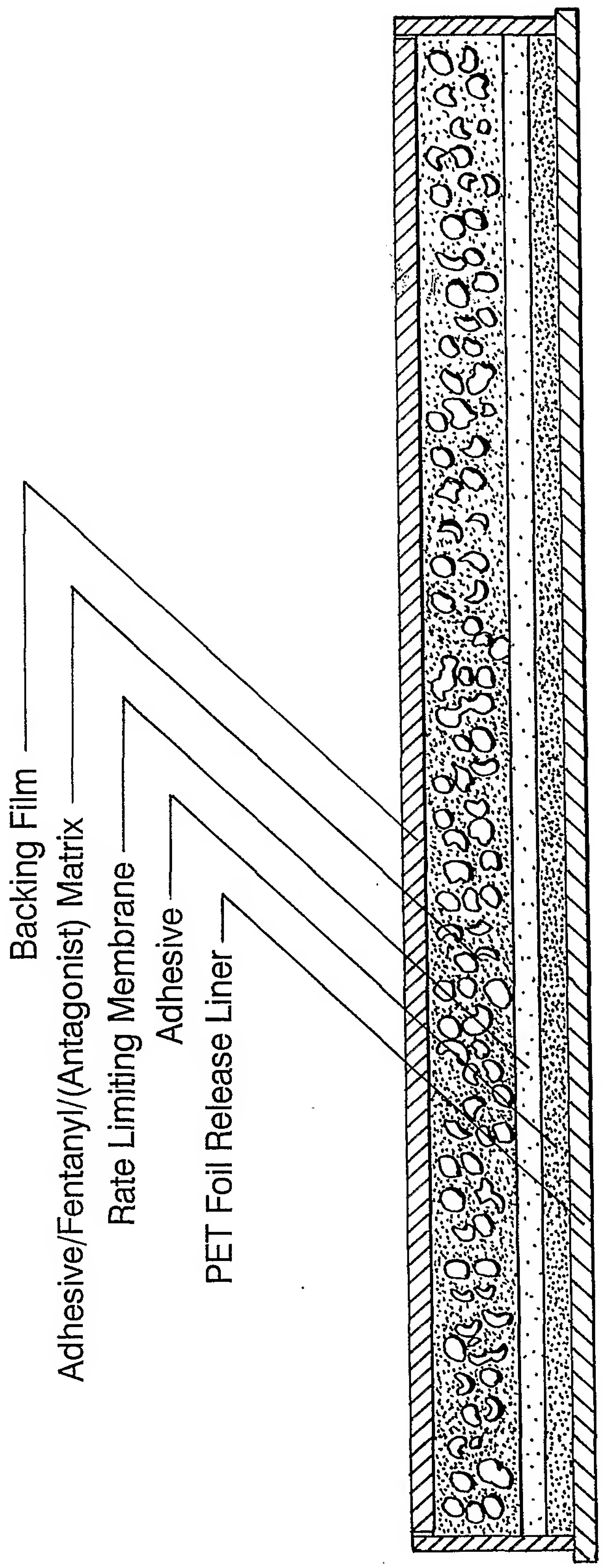
Antagonist and Fentanyl in Different Layers

Figure 1



Antagonist and Barrier Printed on Backing Film

Figure 2



Coated/Complexed Antagonist in Fentanyl/Adhesive Matrix

Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/14073

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61F 13/00
US CL : 424/449
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, ALL DATABASES
Search terms:transdermal opiate, antagonist, cross-linking, beads, matrix.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,096,756 A (GRAIN et al.) 01 August 2000, abstract; col.2, lines 7-54; col.5, lines 18-49; col.6, lines 1-14.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

06 AUGUST 2002

Date of mailing of the international search report

18 SEP 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ISIS GHALI

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★